



Conventional versus drug-eluting bead transarterial chemoembolization: A better option for treatment of unresectable hepatocellular carcinoma

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ABSTRACT

Transarterial chemoembolization (TACE) is a minimally invasive procedure involving intra-arterial catheter-based chemotherapy to selectively administer high doses of cytotoxic drugs to the tumor bed along with ischemic necrosis induced by arterial embolization. Chemoembolization forms the essential core of management in patients with hepatocellular carcinoma (HCC) who are not suitable for curative therapies such as transplantation, resection, or percutaneous ablation. TACE of hepatic cancer(s) has proven to be helpful in achieving local tumor control, and has supported the ability to prevent tumor progression, prolong patient life, and manage patient symptoms. Recent data have demonstrated that, in patients with single-nodule HCC ≤ 3 cm without vascular invasion, the 5-year overall survival with TACE was found to be comparable with hepatic resection and radiofrequency ablation. Used for several years, Lipiodol continues to play a vital role as a tumor-seeking and radiopaque drug delivery vector in interventional oncology. Efforts have been made to enhance the administration of chemotherapeutic agents to tumors. Compared with conventional TACE, drug-eluting bead TACE is a fairly new drug delivery embolization technique that permits fixed dosing and has the ability to provide sustained release of anticancer agents over a period of time. The present review discusses the basic procedure of TACE and its properties, and the effectiveness of conventional and drug-eluting bead chemoembolization systems currently available or presently undergoing clinical evaluation.

1. Introduction

Hepatocellular carcinoma (HCC) is the most widespread primary hepatic malignancy worldwide. It is the fifth most prevalent carcinoma in the world and the third most prevalent cause of cancer-related death.^{1,2} Hepatic fibrosis, along with cirrhosis, constitute the most frequent causes leading to the development of HCC, with chronic hepatitis C and hepatitis B infections representing other key influences.^{3,4} Typically, HCC has a very poor prognosis because it is often in an advanced stage at the time of diagnosis. The Barcelona Clinic Liver Cancer (BCLC) staging system is broadly used for tumor classification and to assess the key factors that influence long-term prognosis. Therefore, the BCLC system helps to expedite the appropriate selection of patients for specific therapeutic interventions.

With better screening programs, along with advances in imaging techniques for individuals at risk for developing HCC, there has been a surge in the number of cases diagnosed with early stage HCC; consequently, immediate management of these cases has improved survival

rates along with better control in those with chronic liver disease.⁵ Management of early stage HCC currently includes curative therapies and modalities such as liver transplantation, hepatic tumor resection, and radiofrequency ablation. The majority of patients with advanced-stage HCC, however, are not ideal candidates for liver resection due to widespread tumor growth and/or significant impairment of functional reserve of the cirrhotic liver with or without existing portal hypertension; moreover, they may also present with concomitant thrombosis of the portal vein.⁶ Transarterial chemoembolization (TACE) is the standard treatment for patients with intermediate HCC.⁷ TACE is typically performed in patients with multinodular HCCs who would likely not benefit from other curative treatments.⁸ TACE is not performed in patients with severely compromised liver function such as Child-Pugh classification C or late B. Two randomized studies found a significant increase in survival rate in patients with intermediate HCC who were treated with TACE.^{9,10,11}

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2. Objective

The objective of the present article is to review the basic procedure of TACE, its properties, patient selection, and the efficacy of conventional TACE (cTACE) and currently available drug-eluting bead (DEB) TACE (DEB-TACE) systems that are undergoing clinical evaluation in cases of unresectable HCC.

2.1. Patient selection for cTACE and DEB-TACE

cTACE and DEB-TACE play integral roles as treatment modalities in patients with early Child-Pugh stage A and in those with intermediate Child-Pugh Stage-B with multinodular HCC, and performance status of 0 and well-maintained hepatic functioning. cTACE and DEB-TACE are established first-line treatment modalities.^{12,13} Selected patients with elevated liver function, along with mildly reduced performance status, with or without evidence of vascular invasion, can be treated using cTACE and DEB-TACE. However, these populations experience a high incidence of complications, which may include liver failure.^{14,15} c-TACE and DEB-TACE are contraindicated in patients with advanced cirrhosis (Child-Pugh C), performance status > 2, significant extrahepatic tumor burden, and those with medically refractory hepatic encephalopathy. Relative contraindications to cTACE and DEB-TACE include tumors within the main portal vein, biliary obstruction, total bilirubin >4, serum creatinine >2, and significant arteriovenous tumor shunting.⁶

3. TACE

TACE is a minimally invasive therapeutic procedure that is typically endorsed as a first-line treatment for intermediate-stage HCC (BCLC stage B).¹⁶ TACE can also be used as a bridge therapy to liver transplantation and reduce HCC recurrence after resection.¹⁷ Performed by specially trained interventional radiologists, a series of images are captured using fluoroscopy to evaluate the path of blood vessels feeding the tumor. This may also involve the use of a contrast material to map the pathway of the vessels. Under fluoroscopic guidance, a catheter is introduced into the common femoral artery—preferably the right common femoral artery—via a small incision of the skin. The celiac trunk is cannulated under fluoroscopic guidance, after which cannulation of the hepatic artery is performed. As soon as the catheter is placed in the branches of the artery that feed the tumor, anti-cancer drugs and embolic agents are mixed and introduced. Additional images are captured to verify whether the entire tumor is adequately treated. After completion of the procedure, the catheter is removed and bleeding, if any, is stopped via application of pressure over the incision.

In TACE, the desired therapeutic effect is achieved through a dual mechanism of action in which a catheter and microcatheter system are guided into the hepatic arterial tree or accessory branches that feed the tumor, and the embolic agent(s) acts by inducing ischemic effects and local hypoxia in the targeted tumor tissue.^{8,18,19,20} Higher concentrations of the chemotherapeutic drug are delivered to the targeted tumor tissue via intra-arterial infusion rather than the typical systemic route. In TACE, the effects of targeted chemotherapy and ischemic necrosis induced by arterial embolization occur.^{19,20} The liver, due to its dual blood supply consisting of an artery (the hepatic artery) and a large vein (the portal vein), is distinct. Normally, the liver receives 75% of its blood supply via the portal vein and the remaining 25% via the hepatic artery. However, once a tumor develops in the liver, it receives the majority of its blood supply through the hepatic artery. Chemotherapeutic drugs are introduced into the hepatic artery to target the tumor directly, leaving most of the healthy liver tissue unaffected. When the artery is obstructed by chemotherapeutic drugs and embolic agents, blood is no longer delivered to the tumor, whereas the liver continues to draw its blood supply through the portal vein. This also permits higher doses of the anti-cancer medications to be in contact with the tumor for prolonged periods. Compared with cTACE, DEB-TACE is a newer method of

administering chemotherapeutic drugs during TACE. It involves the use of special beads preloaded with chemotherapeutic medication (i.e., DEBs). Once these beads are introduced into the arteries of the liver, they gradually release the medication to treat the tumor. Increased vascular permeability inside the targeted tumor tissue occurs, which is a result of vascular endothelial growth factor secretion induced by hypoxia caused by intra-arterially infused chemotherapeutic drugs. Leaky vessels, along with cell membrane dysfunction induced via hypoxia and stagnation of blood flow cause higher intracellular deposition of the chemotherapeutic drug and retention of large amounts of intra-hepatic concentrations of the drug. As a consequence of these modifications, decreased side effects and toxicity have been noted in response to these drugs because lower concentrations of the chemotherapeutic agent are directed into the systemic circulation, thus yielding the desired results.⁶

3.1. cTACE

The embolic agent used in cTACE is lipiodol, which is a derivative of poppy seed oil, and delivers the preferred chemotherapeutic drug to the proposed target. Among others, the most comprehensively used chemotherapeutic agents include doxorubicin, mitomycin C, and cisplatin.^{21,22} The availability of surplus alternatives for formulating chemoembolic mixtures has given rise to significant disparity in treatment practices across centers, thereby making standardization of cTACE difficult. The lipiodol chemotherapy solution is administered via catheter inside the selected hepatic arterial supply distributing the HCC lesion.²¹ After complete infusion of the chemoembolic agent, the catheter is maintained in the same position and bland particles can be further introduced, thereby causing a reduction in the arterial blood flow in the treated segments of the liver.²² This added step is believed to improve the chemotherapy dwell time, leading to increased tumor intracellular uptake and decreased drug washout into the systemic circulation.

3.2. DEB-TACE

TACE using DEBs was introduced to ensure more constant and tumor-specific drug delivery to achieve permanent embolization in which the embolic agent—lipiodol—is replaced with microspheres such as Hepa-Sphere (Merit Medical Systems Inc, South Jordan, UT, USA), DcBead (Boston Scientific, Marlborough, MA, USA), or CalliSpheres (Suzhou Hengrui Callisyn BioMedical Technology Co., Ltd, Suzhou, Jiangsu, China). CalliSphere microspheres are a type of microbeads developed in China and consist of polyvinyl alcohol hydrogel, and have the ability to load positively charged medications, such as doxorubicin, pirarubicin, epirubicin, and Adriamycin, owing to their negatively charged functional groups.²³ A catheter or microcatheter, similar to all catheter-directed locoregional therapies, is positioned in the preferred hepatic arterial supply distributing to the HCC lesion(s) through which DEBs are instilled. The objective of performing DEB-TACE is to achieve stasis of blood flow in the treated hepatic artery supply at the end of infusion.²⁴ Compared to cTACE, data from clinical trials suggest that DEB-TACE may result in the chemotherapeutic agent residing in the tissue for a longer duration, which, in due course, increases exposure of the targeted HCC lesion to the chemotherapeutic drug.^{24,25}

3.3. Outcomes of cTACE and DEB-TACE

Earlier comparative evaluations of cTACE with lipiodol and DEB-TACE in patients with intermediate-stage HCC have resulted in partially contradictory conclusions. The latest meta-analysis of seven studies (n = 693) indicated that both cTACE and DEB-TACE yield similar results, and firmly described a lack of distinction in tumor response between the two procedures, although DEB-TACE resulted in a better patient safety profile.²⁶

Initial phase I/II DEB-TACE studies conducted in China have stressed the properties of doxorubicin-like pharmacokinetics, the dose-limiting

toxicity, safety, and tumor response. In phase I of the trial, the doxorubicin dose was increased from 25 mg to 150 mg in cohorts consisting of 3 patients (total of 15 patients). In phase II of the study, 150 mg of doxorubicin was used. Treatment-related adverse events reported were 11.4% and dose-limiting toxicity observed for up to 150 mg doxorubicin was none. No treatment-related deaths were reported, with a mean low peak plasma doxorubicin concentration reported to be 49.4 ± 23.7 ng/ml. After two rounds of TACE, the partial and complete response rates reported were 50% and 0%, respectively, based on Response Evaluation Criteria in Solid Tumors (RECIST) criteria and 63.3% and 6.7%, respectively, according to the modified RECIST criteria at 1 month after the second round of TACE. Subsequently, various small-size phase II study results on TACE with DcBeads in cases of unresectable HCC, mainly with intermediate BCLC stage, have been reported. According to these studies, the general objective response was approximately 59.6–81.8% and 1- and 2-year survival rates were 65–92.5% and 55–88.9%, respectively. The rate of severe procedure-related complications was approximately 3.2%.

A meta-analysis conducted in 2014 by Han et al. compared current cTACE to DEB-TACE in the treatment of HCC and yielded different outcomes. This systematic review included three randomized controlled trials and two case-control studies.¹⁵ In the largest randomized controlled trial conducted by Lammer, the overall population did not demonstrate substantial differences in terms of disease control. On the other hand, subgroup analyses revealed that overall survival and disease control were statistically higher ($P = 0.038$ and $P = 0.026$, respectively) in the DEB-TACE group than in the cTACE group in patients (67%) with more advanced disease (Child-Pugh B, bi-lobar or recurrent disease).²⁷ A meta-analysis by Gao et al.²⁸ demonstrated that DEB-TACE achieved the same tumor response as cTACE in terms of tumor response, while a meta-analysis by Facciorusso et al.²⁹ concluded similar efficacy and safety results between the two treatments, with only a non-significant trend in favor of DEB-TACE. Finally, a recent systemic review by Xie et al.³⁰ and a meta-analysis by Facciorusso et al.²⁹ reported that none of the treatment regimens were superior to the other in terms of overall survival and safety profile. From these results, DEB-TACE has demonstrated better—or at least similar—results in studies comparing DEB-TACE and cTACE. Furthermore, we may conclude that DEB-TACE could improve the clinical effectiveness in patients with more advanced HCC and be safer in high-risk patients.

For advanced HCCs, such as BCLC stage C, the use of DEB-TACE has not been well studied. According to the BCLC classification, patients with advanced stage HCC (BCLC-C) are recommended for systemic treatment or palliative therapy. In a small retrospective trial of DEB-TACE for patients with advanced HCC ($n = 80$), the median progression-free survival and overall survival were 5.1 months (95% confidence interval [CI] 4.1–7.7) and 13.3 months (95% CI 10.1–18.6), respectively. In another retrospective study, with treatment of DEB-TACE, the overall median survival was 13.5 months (range, 8.2–18.7 months) and severe adverse events were minimal (1%). In subgroup analysis, survival of patients with Child-Pugh A disease was 17.8 months.³¹ Based on the results of these studies, compared with median survivals of 10.7 months and 6.5 months for the sorafenib groups in the SHARP and Asia-Pacific trials, respectively, it appears that patients with Child-Pugh class A disease may fare better with aggressive locoregional treatment in the form of DEB-TACE than systemic monotherapy with sorafenib. Recently, Printer et al.³² reported higher survival in patients with advanced stage disease (BCLC-C) treated with cTACE (9.2 months) than in those treated with sorafenib (7.4 months) ($P = 0.377$). These results suggest that cTACE and DEB-TACE are also as effective as sorafenib in the treatment of advanced HCC.

A study by Liang et al. demonstrated the patients treated with Calispher microspheres TACE (CSM-TACE) achieved better treatment response when compared with that of cTACE. Additional multivariate logistic regression model investigation revealed that CSM-TACE cases individually correlated with a better objective response rate, and no

difference in overall survival was observed between cTACE and CSM-TACE. CSM-TACE was recognized as an independent prognostic factor for more favorable overall survival in multivariate Cox proportional hazard regression model analysis. Other factors, such as history of alcohol intake, abnormal levels of alkaline phosphatase, and large nodule size (≥ 7 cm) are individual predictors of poor treatment outcomes.³³ Another retrospective cohort study also revealed that there was no difference in the median overall survival in advanced HCC patients with portal vein thrombosis treated with DEB-TACE with LC Beads (Boston Scientific) and patients treated with cTACE.³⁴ However, a retrospective cohort study conducted by Rahman et al. reported that, in patients with unresectable HCC, DEB-TACE yielded a longer median survival time compared with cTACE.³⁵ Furthermore, a meta-analysis revealed increased 1-, 2-, and 3-year survival rates in HCC patients treated with DEB-TACE compared to cTACE, and the 1- and 2-year relapse-free survival rates also increased in patients treated with DEB-TACE.³⁶

4. Conclusion

TACE remains the standard of care for the treatment of intermediate stage HCC. Despite several advances in TACE techniques, radiological response evaluation, and patient selection for TACE, there is room for improvement with regard to therapeutic efficacy. To compensate for the limitations of cTACE, DEB-TACE was introduced as a procedure capable of providing more continual and tumor-selective drug administration and permanent embolization, which enables local administration of high doses of anti-cancer agents to the tumor without an increase in systemic levels. DEB-TACE presented superior—or at least parallel—outcomes compared to cTACE, and exhibited better clinical efficacy and patient safety profile in patients with more radical HCC. In even more advanced HCC (BCLC stage C), it demonstrated parallel results when equated with sorafenib. These conclusions favor the use of DEB-TACE in the treatment of HCC, and may be expandable to more advanced stage HCC in the future. This may be achieved by conducting further clinical trials testing and comparing the outcomes of DEB-TACE and cTACE in well-selected patients. Although the results of contemporary studies demonstrate a slight favor toward DEB-TACE in terms of efficacy, overall survival, and tumor regression, further studies are needed to obtain a clearer insight into their efficiency, and a model needs to be formulated to ensure their implementation and achieve better results in the management of patients with intermediate and advanced stage HCC.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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